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Dermatologic Manifestations of Monogenic Autoinflammatory Diseases

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SYNOPSIS

Autoinflammatory disorders are sterile inflammatory conditions characterized by episodes of early-onset fever, rash and disease-specific patterns of organ inflammation. Mutations in innate immune sensors that include the IL-1 β activating inflammasomes, NLRP3, pyrin and NLRC4, pointed to the importance of innate immune dysregulation leading to excessive production or stimulation of the proinflammatory cytokine, IL-1 β , and provided the concept of targeting proinflammatory cytokines as therapeutic intervention. Recently, increased cytokine amplification loops of Type I interferon and IL-18 signaling are the cause of a spectrum of Type-I IFN mediated diseases (interferonopathies) and IL-18 mediated conditions. Many genetically defined autoinflammatory disorders present with cutaneous neutrophilic inflammation associated with systemic manifestations. Innate danger sensing pathways that include inflammasomes and nucleic acid sensing pathways play critical roles in pathogenesis of IL-1 mediated and IFN-mediated disorders and justify a grouping of the genetically-defined autoinflammatory disorders by cytokine mediators, their clinical manifestations, histologic findings and treatment.

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Introduction

Autoinflammatory disorders are immunedysregulatory conditions characterized by early-onset, sterile systemic inflammatory episodes that include fever, rashes, joint pain and features of disease specific organ inflammation (1). The term “autoinflammatory” was proposed by Daniel Kastner in 1999 after the discovery of the genetic causes of the familial Mediterranean fever (FMF) (2, 3) and of the TNF receptor-associated periodic syndrome (TRAPS) (4).

Over the last 15 years the discovery of the genetic causes for a number of autoinflammatory diseases revealed gain-of-mutations (GOF) in intracellular innate immune sensors (Figure 1A, 1B) including the IL-1 and IL-18 activating inflammasomes: *MEFV*/pyrin, *NLRP3*/cryopyrin and *NLRP4*, the latter also leads to high IL-18 serum levels. Mutations in the NOD-like receptor NOD2/CARD15 cause constitutive NF- κ B activation; and more recently mutations in the viral RIG-I-like receptors (RLRs), *IFIH1/MDA-5* (5) and DDX58 or the adaptor molecule *TMEM173/STING* (6) encoding the stimulator of interferon genes (STING), are all linked to Type-I IFN production and cause autoinflammatory phenotypes. Furthermore, loss-of-function (LOF) mutations in genes (i.e., many of the enzymes) involved in protein or nucleic acid metabolism, cell transport and other cellular homeostatic function can lead to the accumulation of intracellular danger signals. This can trigger innate immune sensors and activate proinflammatory pathways (Figure 1A, 1B). The increased and often constitutive release of the proinflammatory cytokines IL-1 β , Type-I IFN, TNF lead to autocrine cytokine amplification loops and have become the targets for therapies. While targeting IL-1 blockade therapeutically has become the treatment of choice for the IL-1 mediated diseases, targeting TNF is used empirically in some conditions and drugs targeting Type-I IFN or IL-18 are currently being used as compassionate use therapies. Many monogenic autoinflammatory disorders present with characteristic skin rashes and cutaneous neutrophilic inflammation and patients are often referred to dermatologists for evaluation of the dermatologic findings and skin biopsies. This points to the importance of dermatologists being familiar with these conditions as specific treatments can be life-changing for many patients. Below are groupings of autoinflammatory diseases based on dermatologic manifestations and fever patterns that allow a preliminary diagnosis on the basis of the systemic and dermatologic manifestations before genetic testing results have been returned (Box 1 and Table 1).

IL-1-mediated Autoinflammatory Diseases (AIDs)

1. Non-specific maculo-papular rashes with recurrent episodic fever and abdominal pain “Hereditary Periodic Fever Syndromes”

The hereditary fever syndromes are characterized by episodic and periodic high fever attacks that are accompanied by abdominal and or chest pain followed by periods of remission or reduced inflammation. They include FMF, HIDS and TRAPS.

Familial Mediterranean Fever (FMF)—*Familial Mediterranean Fever (FMF)* is an early-onset autosomal recessive disorder due to GOF mutation in *MEFV* gene, which encodes pyrin that leads to unregulated release of pro-inflammatory cytokine such as IL-1 β and uncontrolled inflammation. Autosomal dominant forms of the disease exist. The inflammatory attacks typically last for 3–7 days and recur every 4 to 6 weeks and are accompanied by severe abdominal pain and to a lesser degree chest pain due to sterile serositis. Debilitating myalgia with normal creatine kinase (CK) levels and sometimes synovitis is also seen. During the attacks, inflammatory markers, erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) are highly elevated and may normalize in between attacks. Patients from Armenia, Turkey and Arabian countries with a long-standing history of FMF are at high risk of developing AA amyloidosis leading to renal failure.

Cutaneous manifestations: The prevalence of pathognomonic erysipelas-like erythema (Figure 2A) varies widely among different populations: 21% and 46% in Turks and Jews, whereas 3 and 8% in Arabs and Armenians (7) and occurs on the distal extremities. The lesions present as tender, warm, swollen, and erythematous plaques that are triggered by prolonged walking and subsided within 24–48 hours. Other rarer eruptions include scattered non-specific purpuric papules (8); nodules have also been reported in children with FMF (9).

Dermatopathology: Biopsies of cutaneous eruptions reveal dermal edema with a perivascular and interstitial dermal infiltrate composed of neutrophils and lymphocytes (Figure 2B). Mild hyperkeratosis and acanthosis can be seen in the epidermis (10, 11).

Treatment: Colchicine is used as a first-line therapy to treat attacks and to prevent amyloidosis. IL-1 inhibition is effective but is mainly used in colchicine-refractory cases.

Hyperimmunoglobulinemia D syndrome (HIDS)—*Hyperimmunoglobulinemia D syndrome (HIDS)* is an autosomal recessive disorder caused by LOF mutations in the gene *MVK* encoding for mevalonate kinase, an enzyme involved in the cholesterol synthesis (12). Patients with HIDS present with fever attacks which last from 3 to 7 days; tender cervical lymphadenopathy, arthralgia, non-erosive arthritis, and commonly with abdominal pain; vomiting and diarrhea. Hepatomegaly and splenomegaly are seen in a quarter to a third of patients and serositis is less frequent. During attacks patients have very high inflammatory markers, ESR, CRP, and leukocytosis that may continue to be elevated in between attacks. High serum immunoglobulin D (IgD) may assist in making the diagnosis but can be normal in a quarter of all patients. The frequency of the attacks often decreases with increasing age. Rarely, only about 3% of patients with longstanding disease develop type AA amyloidosis.

Other rare complications include abdominal adhesions from repeated peritonitis and joint contractures.

Cutaneous manifestations: Skin lesions vary with fever attacks and are seen in more than two-thirds of HIDS patients. They include maculopapular, morbilliform, nodular, and purpuric rashes (Figure 2C). Behçet-like aphthae with or without genital ulcerations develop in almost 50% of the patients (13, 14).

Dermatopathology: Biopsies of affected skin show endothelial cell swelling, fibrinoid necrosis of vessel walls, and a perivascular neutrophilic and lymphocytic infiltrate. Slight leukocytoclasia and features of leukocytoclastic vasculitis can be seen. By direct immunofluorescence (DIF), perivascular deposits of IgD and C3 in granular staining pattern are found in skin samples from some patients (15).

Treatment: NSAIDs, prednisone, IL-1 blockade have been the treatments of choice. TNF inhibition (Etanercept) can be effective in some patients in reducing severity of disease flares, but colchicine, thalidomide, cyclosporine are ineffective (16).

TNF-receptor associated periodic syndrome (TRAPS)—*TNF-receptor associated periodic syndrome (TRAPS)* is a dominantly inherited disorder caused by LOF mutations in the *TNFRSF1A* gene encoding TNF-alpha receptor 1 that results in retention of mutant TNF receptor in the Golgi apparatus and an inflammatory reaction that is complex and involves increased TNF and IL-1 production and signaling (17) (18). Patients present with recurrent fever and abdominal pain, pleurisy, joint pain and can resemble FMF attacks. However they are longer and can last from one to several weeks and recur every 4–6 weeks; attacks can be spaced wider. Clinical manifestations include conjunctivitis and periorbital edema (Figure 2F), and rarely uveitis and iritis. Acute-phase reactants, ESR, CRP, haptoglobin, fibrinogen, and ferritin, can be elevated during inflammatory attacks in all hereditary fever syndromes. Autoantibodies to ANA, RF or ANCA are not usually found. Systemic AA amyloidosis with development of nephrotic syndrome and renal failure is a dreaded severe complication of TRAPS.

Cutaneous manifestations: TRAPS patients often complain of focal migratory myalgia that underlies centrifugal, migratory, tender, well-demarcated, blanchable, erythematous plaques often on the lower legs (Figure 2G). The lesions develop during early childhood as warm, urticarial erythematous macules and plaques.

Dermatopathology: On histopathology, a mild perivascular lymphocytic infiltrate is often present in the edematous areas of the papillary dermis. Slight perivascular C3 and C4 deposition in the dermis has been described (19). A fascial biopsy shows no histologic evidence of myositis but a dense inflammatory infiltrate surrounding connective tissue, including focal panniculitis, fasciitis, and perivascular chronic inflammation (20).

Treatment: Corticosteroids and anti-TNF agents suppress the attacks and control the disease activity and severity. IL-1 blockade shows satisfactory responses and has become the

agent of choice in many instances and is beneficial in patients with a high risk for the development of amyloidosis (21) (16, 22). Colchicine is not effective in TRAPS patients.

2. Neutrophilic Urticaria (the Cryopyrin Associated Periodic Syndromes (CAPS))

The three conditions, Familial cold autoinflammatory syndrome (FCAS), Muckle Wells Syndrome (MWS) and Neonatal-onset multisystem inflammatory disease (NOMID) also known as chronic infantile, neurological, cutaneous and articular (CINCA) listed in increasing disease severity are referred to as Cryopyrin- associated Periodic Syndromes (CAPS).

Autosomal dominant GOF mutations in *NLRP3* lead to unchecked inflammasome activation in CAPS patients (23) (24). The hallmarks of all CAPS include a nonpruritic neutrophilic urticaria on the trunk, extremities and face associated with low-grade fevers, conjunctivitis, arthralgia and elevated acute phase reactants during active disease. Inflammatory attacks in NOMID may mimic neonatal sepsis early in life. Ocular manifestations are not always present in FCAS attacks, but conjunctivitis, episcleritis and uveitis are seen in patients with MWS and NOMID. Patients with MWS often develop sensorineural hearing loss in the second and third decade of life. NOMID is the most severe form of CAPS with disease hearing loss developing in the first decade of life. They present with aseptic meningitis with neutrophilic pleocytosis; hydrocephalus, and cognitive impairment can develop in NOMID patient who remain without early appropriate treatment.

Cutaneous manifestations—In FCAS, low ambient temperatures trigger inflammatory attacks, which resolve within a few hours, whereas urticaria (Figure 3A) may develop at birth or within hours of birth in patients with MWS and NOMID and are typically not induced by cold. The skin lesions in patients with FCAS and the other CAPS patients are intermittent, migratory and non-scarring; the ice cube test is negative.

Dermatopathology—Histologically, the epidermis is unaffected in CAPS. Mild edema of the papillary dermis and dilatation of superficial dermal capillaries can be seen. Predominantly neutrophilic, perieccrine and perivascular infiltrates are noted throughout the dermis (Figure 3B, 3C, 3D); there is no evidence of vasculopathy or vasculitis. Histologic findings of neutrophilic infiltrates in lesional skin differ from classical urticarial, where lymphocytes and eosinophils are the predominant inflammatory cells.

Treatment—IL-1 inhibition with anakinra, a recombinant human IL-1 receptor antagonist (FDA approved for NOMID) and long acting blockers (rilonacept and canakinumab, FDA approved for FCAS and MWS) are standard of care. Treatment results in rapid improvement of inflammatory symptoms. Early initiation of treatment is crucial to prevent disease progression and organ damage (16).

IL-18/IL-1-mediated AID

NLRC4-related macrophage activation syndrome (NLRC4-MAS)

NLRC4-related macrophage activation syndrome (NLRC4-MAS) is caused by GOF mutations in *NLRC4*, which encodes a protein that nucleates the *NLRC4* inflammasome.

Disease-causing mutations lead to early-onset fever flares and predispose to the development of macrophage activation syndrome (MAS) (25, 26). In the perinatal period early-onset enterocolitis with periodic fevers can be seen. Characteristic features of MAS flares are caused by uncontrolled macrophage activation and include persistent fever, extreme hyperferritinemia, transaminitis, variable lymphadenopathy and hepatosplenomegaly, raised CRP, initially high then dropping ESR and rapidly progressing pancytopenia that are partially caused by macrophage hemophagocytosis. As MAS progresses, hypertriglyceridemia, and serum fibrinogen, and D-dimer elevation are associated with multi-organ failure. The mortality of untreated MAS is high.

Unlike patients with CAPS and other autoinflammatory diseases, patients with *NLRC4* mutations have extremely high serum IL-18 levels, comparable to levels seen in other conditions that are prone to the development of MAS such as Systemic Juvenile Idiopathic Arthritis (sJIA) and some adult forms of Still's disease (25, 27, 28). Patients can present with variable severity of GI inflammation in early infancy.

Cutaneous manifestations—CUTANEOUS MANIFESTATIONS of *NLRC4*-MAS can vary and include an evanescent rash with dermographism and linear erythema-like lesions (25, 26), other patients present with an urticaria-like rash and fever flares similar to those seen in CAPS patients with *NLRP3* mutations (29).

Dermatopathology—Histology of skin biopsies is not currently available. Histologic exam of a duodenal mucosal biopsy show mixed inflammatory infiltrate in the lamina propria and mild villous blunting (25).

Treatment—Corticosteroids and IL-1 blockade can alleviate inflammatory flares. However, high serum IL-18 levels may persist even after IL-1 inhibition therapy.

3. Pustular skin rashes and episodic fevers

The conditions listed below are a pathogenically heterogeneous group of autoinflammatory disorders that all present with pustulosis.

a. IL-1-mediated pyogenic disorders with sterile osteomyelitis

Deficiency of IL-1 receptor antagonist (DIRA): *Deficiency of IL-1 receptor antagonist (DIRA)* is a severe recessive disorder caused by LOF mutations in *IL1RN*, which encodes the IL-1 receptor antagonist (IL-1Ra) (30–32). Patients present with high elevation of acute phase reactants, multifocal periosteitis, bony overgrowth and sterile painful osteomyelitis. Lesions involve the long bones, frequently the ribs, vertebra and skull. Odontoid involvement can lead to atlantoaxial subluxation.

Cutaneous manifestations: DIRA is characterized by neonatal-onset diffuse pustular dermatitis (Figure 3E) that can appear in crops limited to one area or be generalized.

Dermatopathology: Biopsies of skin lesions of patients with DIRA show dense MPO+ neutrophilic infiltrates in epidermis and superficial dermis (Figure 3F, 3G, 3H), formation of

pustules around the hair shaft, acanthosis and hyperkeratosis. Deep connective tissue may show evidence of vasculitis and perivascular neutrophilic infiltration (30).

Treatment: Anti-inflammatory and “replacement therapy” with recombinant IL-1 receptor antagonist, Anakinra (IL-1RA) is the treatment of choice and leads to complete remission (30–32).

Majeed syndrome: *Majeed syndrome* is caused by recessive LOF mutations in the *LPIN2* gene, which encodes a phosphatase, lipin2, which plays a non-redundant role in phospholipid processing in monocytes and macrophages and in innate immune responses. Patients with Majeed syndrome present with perinatal-onset recurrent osteitis and multifocal sterile osteomyelitis. Patients may present with mild or transfusion-dependent congenital hypochromic microcytic anemia.

Cutaneous manifestations: Skin eruptions are described as “Sweet syndrome” like lesions and other forms of neutrophilic dermatoses, including pustulosis and severe psoriasis (33). Skin lesions can be itchy with serosanguinous discharge. (34)

Dermatopathology: Lesional skin biopsies show dermal neutrophilic infiltrate with edema of upper dermis without histologic evidence of vasculitis.

Treatment: IL-1 blockade is highly efficacious with dramatic improvement of inflammatory symptoms (30–32, 35–37).

b. Partially IL-1-mediated pyogenic disorders

Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA): *Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA)* syndrome is dominantly inherited and is caused by mutations in the *PSTPIP1* gene (38). Arthritis may start in the first decade of life and can be progressively destructive. Elevated levels of acute-phase reactants are seen during disease flares but can be persistently high in patients with severe chronic and recalcitrant disease.

Cutaneous manifestations: Skin eruptions can be triggered by minor trauma and usually begin as violaceous nodules on extremities or face and result in chronic, poor-healing ulcers with undermined borders; severe cystic acnes may heal with scars (Figure 2D, 2E).

Dermatopathology: Histologic findings include inflammatory infiltrates composed of predominantly neutrophils in the dermis and superficial ulcerations.

Treatment: The disease responds partially to systemic glucocorticoids. The pyogenic arthritis is usually responsive to IL-1 inhibition. However, patients with refractory skin lesions may need treatment with TNF-blocking agents (infliximab, adalimumab, etanercept) to obtain control of their skin disease. Optimal treatment still needs to be defined.

Haploinsufficiency of A20 (HA20): *Haploinsufficiency of A20 (HA20)* is caused by autosomal dominant LOF mutations in *TNFAIP3*, leading to a ubiquitylation defect that

results in impaired regulatory function of A20 and upregulation of the NF- κ B signaling pathway and multi-organ inflammation (39). The condition is indistinguishable from the “not genetically-defined” Behçet’s disease, and can be considered to be a monogenic form of Behçet’s disease. Symptoms start in early childhood or in adolescence. *TNFAIP3* gene polymorphisms have been associated with the prevalence of Behçet’s disease in the Chinese Han population (40). Clinical features of HA20 include asymmetrical non-deforming polyarthritis of small and large joints, uveitis, retinal vasculitis, gastrointestinal manifestations such as colitis, diffuse ulcers in oropharynx, colon, ulcer in the terminal ileum and rarely CNS vasculitis. Autoantibodies to ANA, RNP, ds-DNA, lupus anticoagulant can be found.

Cutaneous manifestations: HA20 patients present with oral and genital ulcers, skin eruptions described in the not genetically-defined Behçet’s disease and includes papules, folliculitis, erythema nodosum-like lesions, and pathergy.

Dermatopathology: Histologic findings for patients with HA20 have not been reported, but the spectrum of clinical lesions is similar to what is reported in patients with not yet genetically defined Behçet’s disease and includes folliculitis and erythema nodosum-like lesions. In Behçet’s disease, features of neutrophilic vasculitis and the deposition of fibrinoid material within the vessel walls of arterioles and venules was seen in more than 40% of biopsied samples from patients with Behçet’s disease (41) but it is unknown if this is also a common feature in patients with HA20 Behçet’s.

Treatment: Patients with HA20 respond to colchicine and TNF blockade with infliximab and anti-IL-1 therapy in a refractory case (39).

c. Pyogenic disorders caused by non-IL-1 cytokine dysregulation

Deficiency of IL-36 receptor antagonist (DITRA): *Deficiency of IL-36 receptor antagonist (DITRA)* is an autosomal recessive disorder caused by homozygous or compound heterozygous LOF mutations in *IL36RN*, encoding IL-36 receptor antagonist (IL-36Ra), also known as IL-1F5. DITRA is characterized by recurrent episodes of high-grade fever, generalized pustular lesions, and with elevated ESR, CRP and leukocytosis. IL-36Ra is an antagonist that binds to the IL-36 receptor (IL-36R) and downregulates IL-36 α , - β and - γ signaling, (formerly named IL-1F6, IL-1F8, and IL-1F9). The IL-36R that is highly expressed on keratinocytes and hematopoietic cells and regulates the IL-23/IL-17/IL-22 pathway in the skin (42). Disease flares are triggered by viral, and bacterial infection, menstruation, and pregnancy. Other features include diarrhea with hypernatremia and dehydration followed by feeding difficulties and growth failure in young children. Gastric ulcers were also reported in a patient with DITRA.

Cutaneous manifestations: Patients present with generalized scaly erythematous pustular eruptions, erythematous scaly plaques. The initial erythematous pustular lesions often precede desquamation of the leg and scalp. Psoriasis vulgaris, acral pustular lesions of the digits, nail dystrophy, impetigo herpetiformis, geographic tongue and scrotal lesions have been described. (43)

Dermatopathology: Skin biopsies show spongiosis with subcorneal pustules, acanthosis and parakeratosis, a dense neutrophilic and lymphocytic infiltrate with CD3+ and CD8+ T cells. Dermal CD68+ and MPO+ cells suggestive of tissue macrophages and neutrophils are noted.

Treatment: Optimal treatment of the disease is still challenging. Different therapeutic agents such as topical steroids, oral glucocorticoids, retinoids, methotrexate, cyclosporine, adalimumab, etanercept, infliximab show variable individual responses. The use of anti-IL17 and anti-IL23 agents may be indicated but has not been reported so far.

CARD14 mediated psoriasis (CAMPS): *CARD14 mediated psoriasis (CAMPS)* is dominantly inherited, by GOF mutations in *CARD14*, caspase recruitment domain family, member 14, that is expressed in keratinocytes and endothelial cells but not in hematopoietic cells. The disease can present as a monogenic form of psoriasis vulgaris, or pustular psoriasis (44) or as pityriasis rubra pilaris (45). Variable disease expression is seen in affected family members belonging to the same family. Mutant CARD14 leads to increased NF- κ B translocation and increased production of chemokines by keratinocytes. It is hypothesized that tissue macrophages produce and secrete IL-23 and recruit and induce Th17 cell differentiation and the release of IL-17A and IL-17F, cytokines that are also produced by CD4+ and CD8+ T cells, $\gamma\delta$ T cells, neutrophils and mast cells. This can induce pro-inflammatory cytokines and chemokines milieu. Their target includes keratinocytes that become more activated (46, 47) and fuel an abnormal amplification loop that further augments keratinocyte activation and inflammatory cell recruitment. Generally, fever and other systemic manifestations are uncommon in the absence of superinfection of the skin in patients with CAMPS.

Cutaneous manifestations: Patients with CAMPS present with a variable clinical severity spectrum from localized plaque and pustular psoriasis to the severe generalized manifestations of familial pityriasis rubra pilaris.

Dermatopathology: Similarly, the histologic features vary and can range from those seen in plaque psoriasis, pustular psoriasis and pityriasis rubra pilaris (PRP). The histologic features of PRP that include acantholysis, hypergranulosis, follicular plugging, and the absence of psoriatic capillary alterations, granular layer diminution, and epidermal pustulation (48) may be considered to be at the severe end of the psoriasis/PRP severity spectrum.

Treatment: The condition can be seen as a monogenic form of psoriasis and responds to the same treatments that are used for moderate-to-severe psoriasis including methotrexate, cyclosporine, anti-TNF agents, IL-12/23p40 inhibitor (ustekinumab) and IL-17A inhibitor (secukinumab) and other drugs targeting IL-17 and IL-23 (49).

Early onset of inflammatory bowel disease (EO-IBD): *Early onset of inflammatory bowel disease (EO-IBD)* is caused by autosomal recessive LOF mutations in either *IL-10RA* or *IL-10RB* gene, encoding IL-1 (50). Patients with this mutation present with severe infantile inflammatory bowel disease, typically in the first 3 months of life, characterized by bloody diarrhea, colonic abscesses, perianal fistula and oral ulcers. Other manifestations include

chronic folliculitis, arthritis, fever, growth retardation and delayed puberty. IL-10 inhibits proinflammatory cytokine release and action by blocking NF- κ B dependent signals and plays a critical role in maintaining mucosal homeostasis. Transmembrane IL-10R is a heterodimer and consists of the IL-10R-alpha and IL-10R-beta subunits that bind IL-10 (51, 52). Colonoscopy shows moderate to severe colitis with an early cobblestone pattern, a mixed inflammatory infiltrate and intermittent deep ulcerations and pseudopolyps.

Cutaneous manifestations: CUTANEOUS MANIFESTATIONS include early-onset recurrent folliculitis and enterocutaneous fistulas.

Treatment: EO-IBD is a severe, therapy-refractory bowel disease. Patients often require surgical interventions including partial or total colectomy (50). Patients with EO-IBD and particularly those with mutations in the *IL-10R* underwent hematopoietic stem cell transplantation (HSCT) and achieved clinical remission (50).

Type-1 IFN-mediated AIDs

A number of conditions present with high type-I IFN production and have been termed interferonopathies (53). Mutations in viral sensors and enzymes regulating nucleic acid metabolism suggest that the accumulation of nucleotides may trigger viral sensors that drive the Type I IFN response in some diseases. However, in other conditions such as CANDLE the molecular pathways leading to the type I IFN response remain unknown. The conditions caused by nucleic acid dysregulation have a predilection for the development of severe neurologic and white matter disease when the disease presents in the first decade of life. The conditions presenting as autoinflammatory syndromes with high IFN scores can be grouped into 2 different categories depending on their cutaneous and vascular manifestations.

4. Vasculopathy and Panniculitis/Lipoatrophy Syndromes

Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated temperature syndrome (CANDLE)—*Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated temperature syndrome (CANDLE)* or Proteasome associated autoinflammatory syndromes (PRAAS) also known as Nakajo-Nishimura syndrome (NNS) and Joint contractures, Muscle atrophy, microcytic anemia and Panniculitis-induced lipodystrophy (JMP) is caused by recessive mutations in *PSMB8*, and digenic mutations involving monoallelic changes in various combinations of *PSMB8*, *PSMB9*, *PSMA3*, *PSMB4*. A monogenic autosomal dominant form with LOF mutations in proteasome maturation protein (POMP) has been seen in one patient leading to impaired degradation of polyubiquitylated proteins and Type-I IFN production (54–59). Mechanisms of pathogenesis are still poorly understood. Clinical features include arthritis, joint contractures, fevers, myositis, hepatosplenomegaly, swelling of distal fingers, conjunctivitis, episcleritis, basal ganglia calcification, mild lymphocytic aseptic meningitis, metabolic syndrome and later in life emaciation due to lipoatrophy and muscle atrophy, and rarely cardiac arrhythmias and cardiomyopathy (58, 59). Transient thrombocytosis or thrombocytopenia, neutropenia, lymphopenia, hypertriglyceridemia and elevated acute phase reactants can be seen with

flares (60). Bone marrow suppression can develop over time with features of myelodysplasia.

Cutaneous manifestations: CANDLE is characterized by early-onset nodular erythematous eruptions (Figure 3 A) on trunk and extremities, facial rashes that include red edematous, heliotrope-like rashes and progressive facial lipoatrophy.

Dermatopathology: Histologic findings include perivascular and interstitial mononuclear inflammatory infiltrates with karyorrhexis in the reticular dermis with extension into the subcutis (Figure 3 B, C). Strong and diffuse MPO and chloroacetate esterase staining in skin biopsies support the presence of myeloid cells (Figure 3 D, E). Intense positivity of CD68, and CD163 indicate the presence of histiocytes and macrophages. Moderate amount of CD123+ cell infiltrates in the dermis represent presence of plasmacytoid dendritic cell (61).

Treatment: Patients respond partially to steroids, but are therapy-refractory to NSAIDs, colchicine, dapsone, methotrexate, tacrolimus, azathioprine, TNF-, IL-1- and IL-6-blocking agents (60). Evidence of a strong IFN response gene signature in CANDLE patients led to the compassionate use of the JAK inhibitor baricitinib that blocks IFN receptor signaling through inhibition of the Janus kinases, JAK1/JAK2 (62).

5. Vasculopathy and/or Vasculitis with Livedo Reticularis Syndromes

a. Without significant CNS disease

STING-associated vasculopathy with onset in infancy (SAVI): *STING-associated vasculopathy with onset in infancy (SAVI)* is caused by de novo GOF mutations in the gene, *TMEM173*, encoding stimulator of interferon genes protein (STING), a major adaptor of interferon signaling (6, 63, 64). Patient present with cold-aggravated skin lesions that start in the first few weeks of life and skin biopsies confirm vasculitis and vascular occlusion. Lesions heal with tissue loss and scarring and are prominent on acral surfaces including fingers and toes, the auricular cartilage, tip of the nose and cheeks, perforation of the nasal septum. Dystrophic nail changes, resorption and gangrene of fingers and toes are seen. The majority of patients have hilar or paratracheal and interstitial lung disease (ILD) with variable severity (6, 65). Patients present with fever and systemic inflammation during flares with elevation of the erythrocyte sedimentation rate and C-reactive protein level. IgM and C3 depositions can be seen in damaged vessels. Low-titer autoantibodies such as p-ANCA, c-ANCA, antiphospholipid antibodies are variable, but do not correlate with the disease activities (6, 65). Later onset and milder phenotypes have been described in one report (63).

Cutaneous manifestations: Patients present with early-onset skin lesions with a chilblain distribution that are worse on cold exposure. Lesions include telangiectasia, pustular, blistering rashes, vasculitic ulcers or plaques (Figure 4F), that predominantly developed on cheeks, nose, fingers, toes, and soles of patients. Large eschars and secondary painful crusts on the cheeks and the tip of the helix were reported and are thought to be secondary to localized superinfection of the skin (6, 65).

Dermatopathology: Histologically, affected skin shows features of small-vessel vasculitis: fibrin deposits, microthrombosis (Figure 4G, 4H). Skin-biopsy samples from some patients show evidence of IgM and C3 depositions (6). Biopsy of telangiectatic plaques obtained from a patient with SAVI revealed rare epidermal apoptotic keratinocytes and perivascular lymphocytic and neutrophilic infiltrates with nuclear dust (leukocytoclasia) throughout the entire dermis without damage to the vessel wall, fibrinoid necrosis and thrombi (Figure 4I). The results of direct immunofluorescence of affected skin were negative (65).

b. With severe CNS disease

Aicardi-Goutières Syndromes (AGS): *Aicardi-Goutières Syndromes (AGS)* is mostly inherited as a recessive disorder caused by LOF mutations in, genes encoding nucleic acid repair enzymes. They include mutations in *TREX1*, a DNA 3' repair exonuclease 1, *RNASEH2A*, *-B* and *-C*, all subunits of ribonuclease H2 enzyme complex, and *SAMHD1*, cellular enzyme SAM domain and HD domain containing protein 1. Autosomal dominant and sporadic forms are caused by heterozygous LOF mutations in *ADARI*, an RNA repair/editing enzyme resulting in haploinsufficiency. More variable disease phenotypes are seen with autosomal dominant GOF mutations in two cytosolic dsRNA sensors, *IFIH1* encoding MDA5 (45) (5) and in *DDX58* encoding RIG-I (64). AGS is characterized by early-onset inflammatory encephalopathy associated with chronic CSF lymphocytosis, and high IFN- α levels in the CSF. Brain Magnetic resonance imaging (MRI) and computer tomography (CT) findings (66) include intracranial calcifications in the white matter, basal ganglia and thalami, ischemic or hemorrhagic strokes, white matter loss resulting in cerebral atrophy and microcephaly. Patients with AGS may present with spasticity, dystonia, large vessel disease including Moya-Moya, stenosis or aneurysms, psychomotor retardation and death in childhood. Patients may have low titer of autoantibodies. Some patients may develop features of autoimmune disorders later in life. Vascular mineral deposits and cortical microinfarctions were occasionally found in postmortem brains. Some heterozygous mutations in *TREX1* and *TMEM173/STING* may cause autosomal dominant forms of sporadic or familial "Chilblain Lupus".

Cutaneous manifestations: CUTANEOUS MANIFESTATIONS include digital vasculitis and or necrosis, chilblains, skin mottling, sometimes with panniculitis, necrotic cheek eruptions, lipoatrophy.

There is currently no treatment for these patients. Immunotherapy with Type-I IFN inhibiting agents is being explored.

Deficiency of adenosine deaminase 2 (DADA2): *Deficiency of adenosine deaminase 2 (DADA2)* is an autosomal recessive disorder caused by compound heterozygous missense mutations in *CECR1*. Patients present with polyarteritis nodosa like lesions, early-onset strokes, peripheral neuropathy, livedo reticularis, Raynaud symptoms. Other features include hypertension, renal infarct, hepatosplenomegaly, portal hypertension, cervical lymphadenopathy and systemic manifestations of chronic inflammation including anemia. Variable low serum immunoglobulin with or without autoantibodies (67–69). Disease severity can vary even within families with the same mutations, ranging from limited skin

eruptions to severe fatal systemic vasculitis. MRI of the brain abnormalities include acute or chronic subcortical lacunar infarct in deep-brain nuclei and the brain stem, indicating small-vessel occlusions (69). Hemorrhagic strokes, in the context of anticoagulation have been seen. Some angiographic studies show aneurysms and stenosis of abdominal arteries (mesentery, celiac, hepatic and renal); renal cortical infarcts or intracranial calcification on brain CT are sometimes seen (70).

Cutaneous manifestations: CUTANEOUS MANIFESTATIONS include livedo reticularis, skin nodules, purpura, some with leg ulcers, Raynaud symptoms.

Dermatopathology: Histologic findings of skin biopsies include a predominantly interstitial inflammatory infiltrate composed of myeloperoxidase, (MPO+) neutrophils and CD68+ macrophages with perivascular CD3+ T lymphocytes (69), intravascular thrombosis and necrotizing arterial vasculitis. Nonspecific leukocytoclastic vasculitis and panniculitis in skin biopsies (70) has been reported. In lesional skin and brain biopsies, endothelial damage on staining by anti-CD31 antibodies and endothelial-cell activation by E-selectin is seen. Endothelialization of the hepatic sinusoids in liver biopsy has been reported (69). In vitro reduced adenosine deaminase 2 (ADA2) activity causes endothelial damage and impaired M2 macrophage differentiation that are hypothesized to lead to vasculopathy and inflammation. An upregulation of interferon-stimulated gene signature in peripheral blood with marked overexpression of neutrophil-derived gene was seen in patients with DADA2 (71).

Treatment: Many patients respond to TNF inhibitors, but only partially to high doses of glucocorticoids. Fresh frozen plasma and hematopoietic stem cell transplantation have been shown to be effective in some patients with deficiency of ADA2. Cytokine inhibitors and cyclophosphamide therapy cannot control severe disease activity. Anticoagulation with aspirin and heparin is not effective; to avoid bleeding complications, anticoagulation is not recommended.

Spondyloenchondrodysplasia with immune dysregulation

(SPENCDI): *Spondyloenchondrodysplasia with immune dysregulation (SPENCDI)* is caused by recessive LOF mutations in the *ACP5* gene encoding tartrate-resistant phosphatase (TRAP). (72) Lack of TRAP activity leads to hyperphosphorylation and constitutive GOF of osteopontin (OPN), a multifunctional protein that plays a role in bone remodeling through osteoclasts and immune regulation through Toll-like receptor 9 (TLR9) (73). Characteristics of this syndrome include short stature, bone dysplasia, neurologic dysfunction including spastic paraparesis, seizures, cerebral atrophy and intracranial calcifications. Many patients developed 3 or more autoimmune diseases during childhood most commonly systemic lupus erythematosus, thrombocytopenia; and antiphospholipid syndrome, hemolytic anemia, hypothyroidism, Sjogren's syndrome, inflammatory myositis. Increased levels of serum interferon-alpha (IFN α) and an upregulation of an interferon signature were noted in patients with SPENCDI. Other features suggesting autoimmune dysregulation include lupus nephritis, arthritis, increased bone mineral density, recurrent

respiratory infections, rarely interstitial lung disease, positive antinuclear and anti-dsDNA antibodies and hypocomplementemia.

Cutaneous manifestations: CUTANEOUS MANIFESTATIONS includes palpable purpura, petechiae on the lower limbs, severe eczema, hyperpigmented macules, vitiligo, Raynaud's phenomenon with dilated loops of capillaries, livedo reticularis. sclerodermatous or acrocyanotic changes of hands and feet with edema, digital vasculitis, which leads to necrosis and amputation.

Dermatopathology: Affected skin biopsies show a perivascular polymorphonuclear infiltrate without evidence of deposition of complement or immunoglobulin, consistent with a nonspecific leukocytoclastic vasculitis.

Treatment: Skin lesions are responsive to oral steroid therapy, chloroquine and cyclophosphamide. Treatment with other immunosuppressive agents such as azathioprine, mycophenolate mofetil and rituximab showed good response (48, 72).

6. Autoinflammatory disorders with granulomatous skin lesions

a. Without significant immunodeficiency

Blau syndrome (pediatric granulomatous arthritis, PGA): *Blau syndrome (pediatric granulomatous arthritis, PGA)* may be a dominantly inherited GOF mutations in *NOD2/CARD15* and can also present sporadically with a *de novo* mutation as “early-onset sarcoidosis”. The triad of organ involvement includes skin, eye and joints. Patients present early in life with fever, ichthyosis-like exanthema and arthritis (Figure 5B) caused by granulomatous synovitis. Ocular manifestations (Figure 5D) include panuveitis, cataract, glaucoma and permanent vision loss. Other manifestations include sialadenitis, lymphadenopathy, transient neuropathies, granulomatous glomerular and interstitial nephritis, pericarditis, hepatic granulomas, splenic involvement and chronic renal failure. Laboratory tests show systemic inflammation with leukocytosis, thrombocytosis and high ESR and CRP.

Cutaneous manifestations: At presentation the rash may present as generalized erythematous micropapular dermatitis. Later the exanthema becomes tan-colored and may present a “dirty” scaly appearance. The later stage of the rash lasts longer and develops into a papulonodular (Figure 5A), tender reddish-brownish, “dirty-looking” and sometimes scaly rash that affects trunk and the extremities symmetrically. Erythema nodosum-like lesions are also described.

Dermatopathology: Histologic findings include an inflammatory infiltrate of typical non-necrotizing non-caseating “sarcoid type” granulomas, composed of epithelioid and multinucleated giant cell granulomas that are typically found in the subpapillar dermis or in the vicinity of a hair follicle. The granulomata are referred to as “Blau granuloma” (Figure 5C). Other findings include leukocytoclastic vasculitis. Non-caseating granulomata are also seen in liver and synovial tissue, but skin biopsies offer a better diagnostic yield (74).

Treatment: Corticosteroids and TNF and IL-1 blockade are used for treatment of severe refractory disease.

b. With variable features of immunodeficiency and significant CNS disease

PLC γ 2-associated antibody deficiency and immune dysregulation (PLAID): *PLC γ 2-associated antibody deficiency and immune dysregulation (PLAID)* is an autosomal dominant disorder characterized by urticarial and or granulomatous skin eruptions, recurrent infections and positive autoantibodies. A subtype of the disease, Autoinflammation and PLC γ 2-associated antibody deficiency and immune dysregulation (APLAID) is dominantly inherited and presents with recurrent erythematous plaques and vesicopustular eruptions, arthralgia, uveitis and recurrent sinopulmonary infections. Skin biopsies show granuloma.

7. Other Autoinflammatory Syndromes

LACC1-mediated monogenic Still's disease—*LACC1-mediated monogenic Still's disease* is an autosomal-recessive form of systemic JIA associated with homozygous missense mutation of *LACC1*, which encodes laccase which are multicopper oxidoreductases that catalyze the oxidation of a variety of phenolic and non-phenolic compounds. Patients present with quotidian fever, associated with erythematous maculopapular rash, symmetric polyarthritis affecting small and large joints and sometimes with tenosynovitis, serositis, organomegaly and lymphadenopathy. Laboratory findings include leukocytosis, thrombocytosis and elevated acute phase reactants. Some patients may have positive ANA, weak rheumatoid factor, but no extractable nuclear antigen. Erosive arthritic changes with joint destruction can be seen on imaging studies. The disease is refractory to different immunosuppressive agents: NSAIDs, systemic corticosteroids, methotrexate and biologic agents including etanercept, adalimumab, tocilizumab and rituximab (75).

CONCLUSION

Monogenic autoinflammatory disorders are caused by dysregulation in innate immune pathways that coordinate immune responses to intracellular and extracellular danger signals. Many AIDs mimic infections or sepsis particularly early in life and rapidly progress to organ damage and death, which makes it imperative to diagnose these conditions early to ensure early appropriate treatment. Most monogenic autoinflammatory disorders present with neutrophilic dermatoses and a careful clinical and histopathologic evaluation of the skin findings, often presents the first clue to a specific diagnosis. The presence of mutations in genes that encode proteins that enucleate inflammasomes and regulate IL-1 β led to the use and approval of IL-1 blocking agents in CAPS. Recently mutations in genes that regulate nucleic acid metabolism and viral sensing lead to increased Type-I IFN production and suggest a role of IFN blocking agents in treating these conditions. Other “cytokine amplification loops” include IL-17 in the skin and IL-18 in the context of the risk of developing macrophage activation syndrome. With therapies targeting dysregulated innate immune pathways becoming increasingly available, a “personalized treatment approach” becomes possible. Furthermore the discovery of novel monogenic genetic diseases points to inflammatory pathways that are dysregulated in more common, genetically complex

inflammatory diseases and lead to the discovery of key regulators in innate immune pathways that may become targets for therapeutic intervention.

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Abbreviations and Acronyms

ADA2	Adenosine Deaminase 2
AID	Autoinflammatory Disease
AGS	Aicardi-Goutières syndrome
ANA	Antinuclear antibody
APLAID	PLC γ 2-associated autoinflammation, antibody deficiency and immune dysregulation
CAMPS	CARD14-mediated psoriasis
CANDLE	Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperatures
CAPS	Cryopyrin associated periodic syndrome
CINCA	Chronic infantile neurologic, cutaneous and arthritis syndrome
CK	Creatinine Kinase
CNS	Central nervous system
CRP	C-reactive protein
DADA2	Deficiency of adenosine deaminase 2 (ADA2)
DIF	Direct Immunofluorescence
DIRA	Deficiency of interleukin 1 receptor antagonist
DITRA	Deficiency of interleukin 36 receptor antagonist
EO-IBD	Early-onset of inflammatory bowel disease
ESR	erythrocyte sedimentation rate
FCAS	Familial cold autoinflammatory syndrome
FDA	Food and Drug Administration
FMF	Familial Mediterranean Fever
GOF	Gain-of-function

HA20	Haploinsufficiency of A20
HIDS	Hyperimmunoglobulinemia D and periodic fever syndrome
IL-1	Interleukin-1
IFN	Interferon
Ig	Immunoglobulin
JMP	Joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy
LOF	Loss-of-function
MAS	Macrophage activation syndrome
MWS	Muckle-Wells syndrome
NNS	Nakajo-Nishimura syndrome
NLR	NOD-Like Receptor
NOMID	Neonatal-onset multisystem inflammatory disease
PAPA	Pyogenic arthritis, pyoderma gangrenosum and acne syndrome
PGA	Pediatric granulomatous arthritis
PLAID	PLAC γ 2-associated antibody deficiency and immune dysregulation
PRAAS	Proteasome associated autoinflammatory syndrome
RLR	RIG-I-Like Receptor
SAVI	Stimulator of interferon genes (STING)- associated vasculopathy with onset in infancy sJIA: Systemic Juvenile Idiopathic Arthritis
SMS	Singleton-Merten Syndrome
SPENCDI	SPondyloENChonDrodysplasia with Immune dysregulation
TNF	Tumor necrosis factor
TRAPS	TNF-receptor-associated periodic syndrome

References

1. de Jesus AA, Canna SW, Liu Y, Goldbach-Mansky R. Molecular mechanisms in genetically defined autoinflammatory diseases: disorders of amplified danger signaling. *Annual review of immunology*. 2015; 33:823–74.
2. French FMFC. A candidate gene for familial Mediterranean fever. *Nature genetics*. 1997 Sep; 17(1): 25–31. [PubMed: 9288094]
3. Localization of the familial Mediterranean fever gene (FMF) to a 250-kb interval in non-Ashkenazi Jewish founder haplotypes. The French FMF Consortium. *American journal of human genetics*. 1996 Sep; 59(3):603–12. [PubMed: 8751861]

4. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell*. 1999 Apr 2; 97(1):133–44. [PubMed: 10199409]
5. Rutsch F, MacDougall M, Lu C, Buers I, Mamaeva O, Nitschke Y, et al. A specific IFIH1 gain-of-function mutation causes Singleton-Merten syndrome. *American journal of human genetics*. 2015 Feb 5; 96(2):275–82. [PubMed: 25620204]
6. Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Montealegre Sanchez GA, et al. Activated STING in a vascular and pulmonary syndrome. *The New England journal of medicine*. 2014 Aug 7; 371(6):507–18. [PubMed: 25029335]
7. Onen F. Familial Mediterranean fever. *Rheumatology international*. 2006 Apr; 26(6):489–96. [PubMed: 16283319]
8. Takahashi T, Fujisawa T, Kimura M, Ohnishi H, Seishima M. Familial Mediterranean fever variant with repeated atypical skin eruptions. *The Journal of dermatology*. 2015 Sep; 42(9):903–5. [PubMed: 25959027]
9. Majeed HA, Quabazard Z, Hijazi Z, Farwana S, Harshani F. The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis). A six-year study *The Quarterly journal of medicine*. 1990 Jun; 75(278):607–16. [PubMed: 2217666]
10. Barzilai A, Langevitz P, Goldberg I, Kopolovic J, Livneh A, Pras M, et al. Erysipelas-like erythema of familial Mediterranean fever: clinicopathologic correlation. *Journal of the American Academy of Dermatology*. 2000 May; 42(5 Pt 1):791–5. [PubMed: 10775856]
11. Azizi E, Fisher BK. Cutaneous manifestations of familial Mediterranean fever. *Archives of dermatology*. 1976 Mar; 112(3):364–6. [PubMed: 1259449]
12. Cuisset L, Drenth JP, Simon A, Vincent MF, van der Velde Visser S, van der Meer JW, et al. Molecular analysis of MVK mutations and enzymatic activity in hyper-IgD and periodic fever syndrome. *European journal of human genetics: EJHG*. 2001 Apr; 9(4):260–6. [PubMed: 11313769]
13. Braun-Falco M, Ruzicka T. Skin manifestations in autoinflammatory syndromes. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG*. 2011 Mar; 9(3):232–46. [PubMed: 21176105]
14. van der Hilst JC, Bodar EJ, Barron KS, Frenkel J, Drenth JP, van der Meer JW, et al. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. *Medicine*. 2008 Nov; 87(6):301–10. [PubMed: 19011501]
15. Boom BW, Daha MR, Vermeer BJ, van der Meer JW. IgD immune complex vasculitis in a patient with hyperimmunoglobulinemia D and periodic fever. *Archives of dermatology*. 1990 Dec; 126(12):1621–4. [PubMed: 2147822]
16. ter Haar NM, Oswald M, Jeyaratnam J, Anton J, Barron KS, Brogan PA, et al. Recommendations for the management of autoinflammatory diseases. *Annals of the rheumatic diseases*. 2015 Sep; 74(9):1636–44. [PubMed: 26109736]
17. Siegel RM, Muppidi J, Roberts M, Porter M, Wu Z. Death receptor signaling and autoimmunity. *Immunologic research*. 2003; 27(2–3):499–512. [PubMed: 12857993]
18. Bulua AC, Simon A, Maddipati R, Pelletier M, Park H, Kim KY, et al. Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). *The Journal of experimental medicine*. 2011 Mar 14; 208(3):519–33. [PubMed: 21282379]
19. Nakamura M, Kobayashi M, Tokura Y. A novel missense mutation in tumour necrosis factor receptor superfamily 1A (TNFRSF1A) gene found in tumour necrosis factor receptor-associated periodic syndrome (TRAPS) manifesting adult-onset Still disease-like skin eruptions: report of a case and review of the Japanese patients. *The British journal of dermatology*. 2009 Oct; 161(4):968–70. [PubMed: 19673872]
20. Hull KM, Wong K, Wood GM, Chu WS, Kastner DL. Monocytic fasciitis: a newly recognized clinical feature of tumor necrosis factor receptor dysfunction. *Arthritis and rheumatism*. 2002 Aug; 46(8):2189–94. [PubMed: 12209524]

21. Gattorno M, Pelagatti MA, Meini A, Obici L, Barcellona R, Federici S, et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. *Arthritis and rheumatism*. 2008 May; 58(5):1516–20. [PubMed: 18438813]
22. Sacre K, Brihaye B, Lidove O, Papo T, Pocard MA, Cuisset L, et al. Dramatic improvement following interleukin 1beta blockade in tumor necrosis factor receptor-1-associated syndrome (TRAPS) resistant to anti-TNF-alpha therapy. *The Journal of rheumatology*. 2008 Feb; 35(2):357–8. [PubMed: 18260167]
23. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nature genetics*. 2001 Nov; 29(3):301–5. [PubMed: 11687797]
24. Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. *Immunity*. 2004 Mar; 20(3):319–25. [PubMed: 15030775]
25. Canna SW, de Jesus AA, Gouni S, Brooks SR, Marrero B, Liu Y, et al. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. *Nature genetics*. 2014 Oct; 46(10):1140–6. [PubMed: 25217959]
26. Romberg N, Al Moussawi K, Nelson-Williams C, Stiegler AL, Loring E, Choi M, et al. Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. *Nature genetics*. 2014 Oct; 46(10):1135–9. [PubMed: 25217960]
27. Shimizu M, Nakagishi Y, Inoue N, Mizuta M, Ko G, Saikawa Y, et al. Interleukin-18 for predicting the development of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *Clinical immunology*. 2015 Oct; 160(2):277–81. [PubMed: 26101092]
28. Ichida H, Kawaguchi Y, Sugiura T, Takagi K, Katsumata Y, Gono T, et al. Clinical manifestations of Adult-onset Still's disease presenting with erosive arthritis: Association with low levels of ferritin and Interleukin-18. *Arthritis care & research*. 2014 Apr; 66(4):642–6. [PubMed: 24124073]
29. Kitamura A, Sasaki Y, Abe T, Kano H, Yasutomo K. An inherited mutation in NLRC4 causes autoinflammation in human and mice. *The Journal of experimental medicine*. 2014 Nov 17; 211(12):2385–96. [PubMed: 25385754]
30. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *The New England journal of medicine*. 2009 Jun 4; 360(23):2426–37. [PubMed: 19494218]
31. Minkis K, Aksentijevich I, Goldbach-Mansky R, Magro C, Scott R, Davis JG, et al. Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis. *Archives of dermatology*. 2012 Jun; 148(6):747–52. [PubMed: 22431714]
32. Reddy S, Jia S, Geoffrey R, Lorier R, Suchi M, Broeckel U, et al. An autoinflammatory disease due to homozygous deletion of the IL1RN locus. *The New England journal of medicine*. 2009 Jun 4; 360(23):2438–44. [PubMed: 19494219]
33. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, Pelet A, et al. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *Journal of medical genetics*. 2005 Jul; 42(7):551–7. [PubMed: 15994876]
34. Majeed HA, Kalaawi M, Mohanty D, Teebi AS, Tunjekar MF, al-Gharbawy F, et al. Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. *The Journal of pediatrics*. 1989 Nov; 115(5 Pt 1):730–4. [PubMed: 2809904]
35. Herlin T, Fiirgaard B, Bjerre M, Kerndrup G, Hasle H, Bing X, et al. Efficacy of anti-IL-1 treatment in Majeed syndrome. *Annals of the rheumatic diseases*. 2013 Mar; 72(3):410–3. [PubMed: 23087183]
36. Schnellbacher C, Ciocca G, Menendez R, Aksentijevich I, Goldbach-Mansky R, Duarte AM, et al. Deficiency of interleukin-1 receptor antagonist responsive to anakinra. *Pediatric dermatology*. 2013 Nov-Dec; 30(6):758–60. [PubMed: 22471702]
37. El-Shanti, H.; Ferguson, P. Majeed Syndrome. In: Pagon, RA.; Adam, MP.; Ardinger, HH.; Wallace, SE.; Amemiya, A.; Bean, LJH., et al., editors. *GeneReviews(R)*. Seattle (WA): 1993.

38. Wise CA, Gillum JD, Seidman CE, Lindor NM, Veile R, Bashiardes S, et al. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. *Human molecular genetics*. 2002 Apr 15; 11(8):961–9. [PubMed: 11971877]
39. Zhou Q, Wang H, Schwartz DM, Stoffels M, Park YH, Zhang Y, et al. Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. *Nature genetics*. 2016 Jan; 48(1):67–73. [PubMed: 26642243]
40. Li H, Liu Q, Hou S, Du L, Zhou Q, Zhou Y, et al. TNFAIP3 gene polymorphisms confer risk for Behcet's disease in a Chinese Han population. *Human genetics*. 2013 Mar; 132(3):293–300. [PubMed: 23161053]
41. Demirkesen C, Tuzuner N, Mat C, Senocak M, Buyukbabani N, Tuzun Y, et al. Clinicopathologic evaluation of nodular cutaneous lesions of Behcet syndrome. *American journal of clinical pathology*. 2001 Sep; 116(3):341–6. [PubMed: 11554161]
42. Tortola L, Rosenwald E, Abel B, Blumberg H, Schafer M, Coyle AJ, et al. Psoriasiform dermatitis is driven by IL-36-mediated DC-keratinocyte crosstalk. *The Journal of clinical investigation*. 2012 Nov; 122(11):3965–76. [PubMed: 23064362]
43. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *The New England journal of medicine*. 2011 Aug 18; 365(7):620–8. [PubMed: 21848462]
44. Harden JL, Lewis SM, Pierson KC, Suarez-Farinas M, Lentini T, Ortenzio FS, et al. CARD14 expression in dermal endothelial cells in psoriasis. *PloS one*. 2014; 9(11):e111255. [PubMed: 25369198]
45. Bursztejn AC, Briggs TA, del Toro Duany Y, Anderson BH, O'Sullivan J, Williams SG, et al. Unusual cutaneous features associated with a heterozygous gain-of-function mutation in IFIH1: overlap between Aicardi-Goutieres and Singleton-Merten syndromes. *The British journal of dermatology*. 2015 Dec; 173(6):1505–13. [PubMed: 26284909]
46. Isailovic N, Daigo K, Mantovani A, Selmi C. Interleukin-17 and innate immunity in infections and chronic inflammation. *Journal of autoimmunity*. 2015 Jun; 60:1–11. [PubMed: 25998834]
47. Reynolds JM, Angkasekwinai P, Dong C. IL-17 family member cytokines: regulation and function in innate immunity. *Cytokine & growth factor reviews*. 2010 Dec; 21(6):413–23. [PubMed: 21074482]
48. Lausch E, Janecke A, Bros M, Trojandt S, Alanay Y, De Laet C, et al. Genetic deficiency of tartrate-resistant acid phosphatase associated with skeletal dysplasia, cerebral calcifications and autoimmunity. *Nature genetics*. 2011 Feb; 43(2):132–7. [PubMed: 21217752]
49. Campa M, Mansouri B, Warren R, Menter A. A Review of Biologic Therapies Targeting IL-23 and IL-17 for Use in Moderate-to-Severe Plaque Psoriasis. *Dermatology and therapy*. 2016 Mar; 6(1): 1–12. [PubMed: 26714681]
50. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schaffer AA, Noyan F, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *The New England journal of medicine*. 2009 Nov 19; 361(21):2033–45. [PubMed: 19890111]
51. Shouval DS, Biswas A, Goettel JA, McCann K, Conaway E, Redhu NS, et al. Interleukin-10 receptor signaling in innate immune cells regulates mucosal immune tolerance and anti-inflammatory macrophage function. *Immunity*. 2014 May 15; 40(5):706–19. [PubMed: 24792912]
52. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. *Annual review of immunology*. 2001; 19:683–765.
53. Briggs TA, Rice GI, Adib N, Ades L, Barete S, Baskar K, et al. Spondyloenchondrodysplasia Due to Mutations in ACP5: A Comprehensive Survey. *Journal of clinical immunology*. 2016 Apr; 36(3):220–34. [PubMed: 26951490]
54. Brehm A, Liu Y, Sheikh A, Marrero B, Omoyinmi E, Zhou Q, et al. Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. *The Journal of clinical investigation*. 2016 Feb 1. 126(2):795.
55. Tufekci O, Bengoa S, Karapinar TH, Ataseven EB, Irken G, Oren H. CANDLE syndrome: a recently described autoinflammatory syndrome. *Journal of pediatric hematology/oncology*. 2015 May; 37(4):296–9. [PubMed: 25036278]

56. Agarwal AK, Xing C, DeMartino GN, Mizrachi D, Hernandez MD, Sousa AB, et al. PSMB8 encoding the beta5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. *American journal of human genetics*. 2010 Dec 10; 87(6):866–72. [PubMed: 21129723]
57. Kanazawa N, Arima K, Ida H, Yoshiura K, Furukawa F. Nakajo-Nishimura syndrome. *Nihon Rinsho Men'eki Gakkai kaishi = Japanese journal of clinical immunology*. 2011; 34(5):388–400. [PubMed: 22041427]
58. Arima K, Kinoshita A, Mishima H, Kanazawa N, Kaneko T, Mizushima T, et al. Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome. *Proceedings of the National Academy of Sciences of the United States of America*. 2011 Sep 6; 108(36):14914–9. [PubMed: 21852578]
59. Kitamura A, Maekawa Y, Uehara H, Izumi K, Kawachi I, Nishizawa M, et al. A mutation in the immunoproteasome subunit PSMB8 causes autoinflammation and lipodystrophy in humans. *The Journal of clinical investigation*. 2011 Oct; 121(10):4150–60. [PubMed: 21881205]
60. Liu Y, Ramot Y, Torrelo A, Paller AS, Si N, Babay S, et al. Mutations in proteasome subunit beta type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis and rheumatism*. 2012 Mar; 64(3):895–907. [PubMed: 21953331]
61. Torrelo A, Colmenero I, Requena L, Paller AS, Ramot Y, Richard Lee CC, et al. Histologic and Immunohistochemical Features of the Skin Lesions in CANDIE Syndrome. *The American Journal of dermatopathology*. 2015 Jul; 37(7):517–22. [PubMed: 26091509]
62. Almeida de Jesus A, Goldbach-Mansky R. Monogenic autoinflammatory diseases: concept and clinical manifestations. *Clinical immunology*. 2013 Jun; 147(3):155–74. [PubMed: 23711932]
63. Jeremiah N, Neven B, Gentili M, Callebaut I, Maschalidi S, Stolzenberg MC, et al. Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. *The Journal of clinical investigation*. 2014 Dec; 124(12):5516–20. [PubMed: 25401470]
64. Crow YJ, Manel N. Aicardi-Goutieres syndrome and the type I interferonopathies. *Nature reviews Immunology*. 2015 Jul; 15(7):429–40.
65. Munoz J, Rodiere M, Jeremiah N, Rieux-Laucat F, Oojageer A, Rice GI, et al. Stimulator of Interferon Genes-Associated Vasculopathy With Onset in Infancy: A Mimic of Childhood Granulomatosis With Polyangiitis. *JAMA dermatology*. 2015 Aug; 151(8):872–7. [PubMed: 25992765]
66. La Piana R, Uggetti C, Roncarolo F, Vanderver A, Olivieri I, Tonduti D, et al. Neuroradiologic patterns and novel imaging findings in Aicardi-Goutieres syndrome. *Neurology*. 2016 Jan 5; 86(1):28–35. [PubMed: 26581299]
67. Kastner DL, Zhou Q, Aksentijevich I. Mutant ADA2 in vasculopathies. *The New England journal of medicine*. 2014 Jul 31; 371(5):480–1.
68. Segel R, King MC, Levy-Lahad E. Mutant ADA2 in vasculopathies. *The New England journal of medicine*. 2014 Jul 31. 371(5):481.
69. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. *The New England journal of medicine*. 2014 Mar 6; 370(10):911–20. [PubMed: 24552284]
70. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. *The New England journal of medicine*. 2014 Mar 6; 370(10):921–31. [PubMed: 24552285]
71. Belot A, Wassmer E, Twilt M, Lega JC, Zeef LA, Oojageer A, et al. Mutations in CECR1 associated with a neutrophil signature in peripheral blood. *Pediatric rheumatology online journal*. 2014; 12:44. [PubMed: 25278816]
72. Briggs TA, Rice GI, Daly S, Urquhart J, Gornall H, Bader-Meunier B, et al. Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. *Nature genetics*. 2011 Feb; 43(2):127–31. [PubMed: 21217755]

73. Shinohara ML, Lu L, Bu J, Werneck MB, Kobayashi KS, Glimcher LH, et al. Osteopontin expression is essential for interferon-alpha production by plasmacytoid dendritic cells. *Nature immunology*. 2006 May; 7(5):498–506. [PubMed: 16604075]
74. Wouters CH, Maes A, Foley KP, Bertin J, Rose CD. Blau syndrome, the prototypic autoinflammatory granulomatous disease. *Pediatric rheumatology online journal*. 2014; 12:33. [PubMed: 25136265]
75. Wakil SM, Monies DM, Abouelhoda M, Al-Tassan N, Al-Dusery H, Naim EA, et al. Association of a mutation in LACC1 with a monogenic form of systemic juvenile idiopathic arthritis. *Arthritis & rheumatology*. 2015 Jan; 67(1):288–95. [PubMed: 25220867]

KEY POINTS

- Monogenic autoinflammatory disorders are hyperinflammatory conditions caused by single-gene mutations in innate immune regulatory pathways. They often present in infancy or early childhood; some can mimic infection or sepsis.
- Recognizing the clinical and histologic features is essential in initiating genetic testing, appropriate referral to make an early diagnosis, and to begin aggressive treatment to prevent organ damage and life-threatening consequences.
- Patients with IL-1-mediated disorders present with neutrophilic urticaria, pustulosis, migratory rash, whereas IFN-mediated disorders may present with panniculitis, livedo reticularis or vasculitis.
- Anti-IL-1 therapy is the standard of care in treating the cryopyrinopathies (CAPS), and DIRA and other IL-1 mediated conditions including FMF, HIDS, TRAPS.
- Discoveries of the genetic cause of novel autoinflammatory diseases suggest a role for Type I IFN, IL-17 and IL-18; several have uncovered novel targets for therapeutic intervention.

Box 1**Dermatologic Manifestations of Monogenic Autoinflammatory Diseases****1. Non-Specific Maculopapular Rashes with Recurrent Episodic Fever and Abdominal Pain (Hereditary Periodic Fever Syndrome)**

Recurrent Fever Attacks of Short Duration (typically < 7 days)

- FMF: Familial Mediterranean Fever
- HIDS: Hyperimmunoglobulinemia D with periodic fever syndrome/Mevalonate kinase deficiency

Recurrent Fever Attacks of Longer Duration (typically >7 days)

- TRAPS: TNF receptor associated periodic syndrome

2. Neutrophilic Urticaria (the Cryopyrin Associated Periodic Syndrome (CAPS))

Recurrent Fever Attacks of Short Duration (typically <24 hours)

- CAPS/FCAS: Familial Cold Autoinflammatory Syndrome
- CAPS/MWS: Muckle-Wells Syndrome

Continuous Low Grade Fever

- CAPS/NOMID: Neonatal Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurological Cutaneous and Articular Syndrome (CINCA)
- IL-18 and IL-1-mediated AID: NLRC4-related Macrophage Activation Syndrome (NLRC4-MAS)

3. Pustular Skin Rashes and Episodic Fevers**a. IL-1-mediated pyogenic disorders with sterile osteomyelitis**

- DIRA: Deficiency of Interleukin-1 Receptor Antagonist
- Majeed syndrome

b. Partially IL-1-mediated pyogenic disorders

- PAPA: Pyogenic sterile Arthritis, Pyoderma gangrenosum and Acne syndrome
- HA20: Haploinsufficiency of A20 (monogenic form of Behçet's disease)

- c.** Pyogenic disorders caused by non-IL-1 cytokine dysregulation
- DITRA: Deficiency of IL-36 receptor antagonist
 - CAMPS: CARD14- mediated psoriasis (monogenic form of psoriasis)
 - EO-IBD: Early-onset of inflammatory bowel disease
- 4.** Vasculopathy and Panniculitis/Lipoatrophy Syndromes
- CANDLE: Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated temperature syndrome or Proteasome associated autoinflammatory syndromes (PRAAS)
- 5.** Vasculopathy and/or Vasculitis with Livedo Reticularis Syndromes
- a.** Without significant CNS disease
- SAVI: STING-associated vasculopathy with onset in infancy
- b.** With severe CNS disease
- AGS: Aicardi-Goutières Syndromes
 - DADA2: Deficiency of adenosine deaminase 2
 - SPENCDI: Spondyloenchondrodysplasia with immune dysregulation
- 6.** Autoinflammatory Disorders with Granulomatous Skin Diseases
- a.** Without significant immunodeficiency
- Blau syndrome (pediatric granulomatous arthritis, PGA)
- b.** With variable features of immunodeficiency and significant CNS disease
- PLC γ 2 associated antibody deficiency and immune dysregulation (PLAID): Cold-induced urticaria and or granulomatous rash
- 7.** Other Autoinflammatory Syndromes
- *LACCI*-mediated monogenic Still's disease

Figure 1.

IL-1-mediated (A) and IFN Type I-mediated (B) autoinflammatory diseases (AIDs) and their genetic causes. Abbreviations used: PRR, Pattern recognition receptor (PRR), TLRs, Toll-like receptors, CAPS, cryopyrin-associated periodic syndrome (FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease); FMF: familial Mediterranean fever; DIRA, deficiency of interleukin-1 receptor antagonist; NLRC4-MAS (macrophage activation syndrome) (also IL-18 mediated); HIDS, hyperimmunoglobulinemia D and periodic fever syndrome; TRAPS, TNF receptor-associated periodic syndrome. Type I IFN-mediated: SMS, Singleton–Merten syndrome; SAVI, STING-associated vasculopathy with onset in infancy; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; PRAAS, proteasome-associated autoinflammatory syndrome; SPENCDI, Spodlyenchondrodysplasia with immune dysregulation; AGS, Aicardi–Goutières syndrome 1–7

Adapted from Almeida de Jesus A, Goldbach-Mansky R. Genetically defined autoinflammatory diseases. Oral Dis 2016;doi: 10.1111/odi.12448; with permission.

Figure 2.

A. FMF: well-demarcated, swollen, bright erythematous erysipelas-like skin eruption on right ankle. **B.** Histology of skin biopsy of affected skin from a patient with FMF showed a mild perivascular chronic inflammatory infiltrate in dermis. **C.** HIDS: Diffuse erythematous macules and papules over both palms, arms, legs and trunk (not shown) during fever attack. **D.** Pyoderma gangrenosum in PAPA: a large ulcerated lesion with granulation tissue and purulent exudate at the ulcer base. **E.** PAPA: severe cystic acne with hypertrophic scars. **F.** TRAPS: Periorbital edema. **G.** Erythematous patch on the leg of a patient with TRAPS. **FMF:** Familial Mediterranean Fever, **HIDS:** Hyperimmunoglobulinemia D syndrome, **PAPA:** Pyogenic sterile arthritis, pyoderma gangrenosum and acne, **TRAPS:** TNF-receptor associated periodic syndrome.

Figure 3. Cutaneous manifestations and Dermatopathology of NOMID (A through D) and DIRA (E through H)

A. Diffuse erythematous papules and plaques of urticarial rash of a patient with NOMID. **B.** Skin-biopsy section from a patient with NOMID showing perivascular neutrophilic infiltrates in the superficial dermis and surrounding sweat glands (**C**). **D.** MPO+ (mature neutrophils) cellular inflammatory infiltrates (in dark brown) in dermis. **E.** Erythematous patch with papules, vesicles and pustules in a patient with DIRA. **F, G.** Intracorneal and intraepidermal neutrophilic microabscesses in the affected skin of DIRA. **H.** Dense MPO+ cells (in dark brown) within an intraepidermal abscess. **NOMID:** Neonatal-onset multisystem inflammatory disease. **DIRA:** Deficiency of interleukin 1 receptor antagonist.

Figure 4. Cutaneous manifestations and Dermatopathology of CANDLE (A through E) and SAVI (F through I)

A. Indurated, erythematous nodule in a CANDLE patient. **B.** Deep dermal and subcutaneous inflammatory infiltrates. **C.** Neutrophil inflammatory infiltrate in subcutaneous adipose tissue. **D.** MPO+ (neutrophil/myeloid precursor cell in dark brown) cell infiltration in interstitium and near blood vessels. **E.** Perivascular and subcutaneous MPO+ cell infiltrates in CANDLE. **F.** Violaceous vasculitic plaques on the hand of a patient with SAVI. **G, H.** Dense inflammatory infiltrate with fibrinoid necrosis of vessel wall and nuclear debris in dermis and subcutis. **I.** Perivascular and transmural MPO+ cell infiltrate. **CANDLE:** Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperatures. **SAVI:** Stimulator of interferon genes (STING)- associated vasculopathy with onset in infancy.

Figure 5.

PGA or Blau syndrome: **A.** Numerous 1- to 2-mm, red-brown to pinkish tan, flat-topped papules on the trunk and extremities. **B.** Non-erosive arthritis. **C.** Histology of skin biopsy shows (100× original magnification) chronic granulomatous inflammation in dermis, with multiple non-necrotizing granulomas and scattered lymphocytes throughout the dermis. The overlying epidermis is unremarkable and the papillary dermis is uninvolved; 400× original magnification: The non-necrotizing (sarcoid type) granulomas are composed of histiocytes/tissue macrophages with multinucleated giant cells and a peripheral rim of lymphocytes. **D.** Anterior synechiae in a patient with Blau syndrome who had cataract with chronic uveitis. PGA: Pediatric granulomatous arthritis.

Table 1

Clinical Features of IL-1-mediated vs IFN-mediated Autoinflammatory Disorders (AIDs)

IL-1-MEDIATED AIDs	IFN-MEDIATED AIDs
SYSTEMIC	
CRP closely correlates with disease activity	CRP only elevated in severe disease
Granulocytosis with flares	Lymphopenia, leukopenia with flares
CNS	
Aseptic neutrophilic meningitis	Mild lymphocytic meningitis
Arachnoid adhesions (severe disease)	Basal ganglion calcifications, CNS vasculopathy, white matter disease
OTHER ORGAN INVOLVEMENTS	
SKIN, VESSELS: Neutrophilic dermatitis (Urticaria-like with mature neutrophilic infiltrates)	Panniculitis ("immature neutrophils"), lipoatrophy, vasculitis (chilblain-like lesions), Microthrombotic disease
LUNG/HEART: Serositis, pericarditis	Pulmonary fibrosis/interstitial lung disease, HTN, Pulmonary HTN
MSK: Osteomyelitis, bony overgrowth, fasciitis	Myositis
ENT: Hearing loss (inflammatory)	NA
EYES: Conjunctivitis, anterior uveitis	Glaucoma, episcleritis
SEROLOGY: 40% lupus anticoagulant positive	Some with increased autoantibodies

IL-1: Interleukin 1, IFN: Interferon, CRP: C-reactive protein, CNS: Central Nervous System, HTN: Hypertension, MSK: Musculoskeletal manifestations, ENT: Ear, Nose, Throat, NA: not applicable

Adapted from Canna SW, Goldbach-Mansky R. New monogenic autoinflammatory diseases—a clinical overview. *Semin Immunopathol* 2015;37(4):387–94; with permission.